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Chapter 51: Epilepsy

INTRODUCTION

- *Epilepsy* is a common neurological condition marked by recurrent seizures of varying types and causes, often leading to neurobiological, cognitive, psychological, and social effects. *Status epilepticus* is a neurological emergency where seizures last over 5 minutes or continue for more than 30 minutes, risking long-term effects.

CLINICAL PRESENTATION

- **Figure 51-1** shows the International League Against Epilepsy (ILAE) framework for the classification of seizure types.
- Seizures range from intense involuntary repetitive muscular contractions (ie, convulsions) to subtle sensory or consciousness changes. The new classification is based on seizure origin, the patient's level of awareness during the seizure, and other features.
- Seizures are classified by onset as: (1) focal (starting in one side of the brain), (2) generalized (affecting both sides), and (3) unknown onset, which can be reclassified later when it becomes clear how the seizures began.
- In focal aware seizures, patients stay aware of themselves and their surroundings, with possible motor or nonmotor symptoms like those in focal impaired awareness seizures.
- In focal impaired awareness seizures, awareness is reduced at some point; patients may respond inappropriately during the seizures and often can't recall the event afterward.
- Motor signs include:
    - ✓ Automatisms: automatic behaviors (eg, lip smacking, picking at clothing)
    - ✓ Atonic: loss of muscle tone, goes limp
    - ✓ Clonic: rhythmic jerking/twitching
    - ✓ Spasm: trunk flexion
    - ✓ Hyperkinetic: thrashing or pedaling movements
    - ✓ Myoclonic: irregular jerking
    - ✓ Tonic: stiffening (extension or flexion)
- Non-motor signs include:
    - ✓ Autonomic: flushing, sweating, piloerection, salivation, pallor
    - ✓ Behavior arrest: pausing, freezing, activity arrest
    - ✓ Cognitive: language problems, thinking problems, memory phenomenon, and feelings of familiarity (déjà vu) or unfamiliarity (jamais vu)
    - ✓ Emotion: feelings of fear, depression, joy, anger, extreme aberration of behavior

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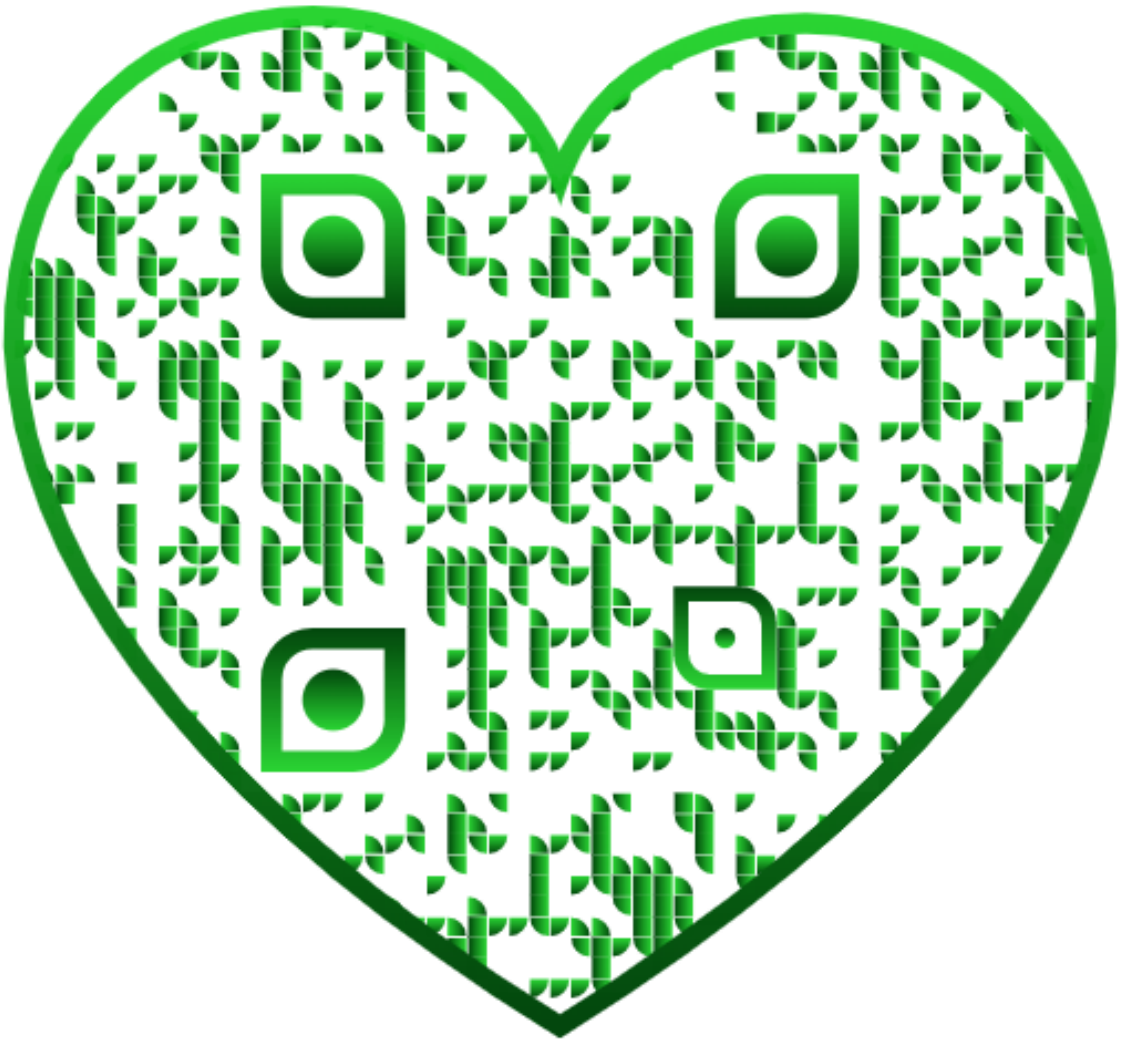


✓ Sensory: numbness, tingling, sounds (ringing/buzzing), smells, tastes, visions (hallucinations), vertigo

- Focal to bilateral tonic-clonic seizures spread to both sides, causing tonic-clonic convulsions and impaired awareness.
- Motor signs include:

  ✓ Tonic clonic: sudden sharp tonic stiffening of muscles with a subsequent period of clonic movements such as rhythmic jerking of arms and legs (previously called “grand mal”)

  ✓ Clonic: rhythmic jerking or twitching of arm, shoulder, face, or leg

  ✓ Myoclonic: arrhythmic jerking of arm, shoulder, face, or leg

  ✓ Atonic: loss of tone, going limp

  ✓ Epileptic spasms: trunk flexion

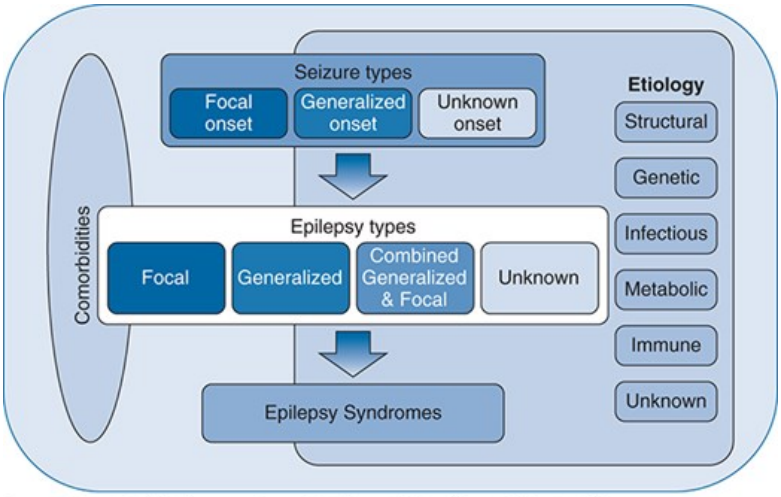
- Non-motor/absence signs include:

  ✓ Typical: sudden arrest of behavior, blank stare with brief upward rotation of the eyes lasting 2–30 seconds

  ✓ Eyelid myoclonia: lid jerks

FIGURE 51-1

ILAE framework for classification of seizure types—expanded version.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Lisa M. Holle, Cecily V. DiPiro: *DiPiro's Pharmacotherapy Handbook, 13th Edition*
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DIAGNOSIS

- Ask the patient and family about seizure characteristics, triggers, frequency, duration, timing, aura, consciousness, ictal, and postictal state. Exams and labs may find the cause.
- Epilepsy is diagnosed if a person has: (1) two or more unprovoked seizures over 24 hours apart; (2) one unprovoked seizure with a ≥60% risk of recurrence over 10 years; or (3) an epilepsy syndrome diagnosis.
- Serum prolactin may rise briefly after tonic-clonic seizures. Measuring it within 10–20 minutes can help distinguish seizures from pseudoseizures, but not from syncope.

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- Laboratory tests can rule out treatable, nonepileptic causes of seizures like hypoglycemia, electrolyte imbalances, and infections.
- Electroencephalogram (EEG) helps diagnose seizure disorders but shows epileptiform activity in only about 50% of epilepsy cases. Brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) can reveal structural lesions to aid diagnosis.

TREATMENT

- Goals of Treatment: To control or reduce seizures, minimize medication adverse effects, and support compliance for the best possible quality of life, thereby balancing seizure control with tolerability, managing comorbidities. Medication adverse effects, comorbidities (eg, anxiety and depression), and social factors (eg, driving, job security, relationships, and social stigma) significantly impact quality of life.

NONPHARMACOLOGIC THERAPY

- Nonpharmacologic therapies (eg, ketogenic diet, vagus nerve stimulation, responsive neurostimulation, deep brain stimulation, and resective surgery, among other modalities) can be tried but the benefits must outweigh risks.

PHARMACOLOGIC THERAPY

- Patients with two or more unprovoked seizures are usually started on antiseizure medications (ASMs), though some providers may begin treatment after one seizure.
- Start with monotherapy; about 65% of patients can be managed on one ASM, though not all become seizure-free.
- Medication choice depends on seizure type, epilepsy classification, and patient factors such as age, gender, comorbidities, drug interactions, adherence, cost, and urgency. Adherence issues often cause treatment failure. **Figure 51-2** illustrates a suggested algorithm for treating epilepsy.
- Provide the patient with a seizure and medication adverse effect diary.
- ASM dosing is shown in **Table 51-1.**
- Titration to a therapeutic dose usually takes weeks or longer, if sensitive to side effects. Loading doses, given orally or intravenously, may be indicated for those with multiple recent seizures. Clinicians should individualize optimal serum levels, as seizure control may occur outside standard ranges (see Table 51-1).
- Newer ASMs are as effective as older ones and may be better tolerated.
- **Carbamazepine, ethosuximide, gabapentin, levetiracetam, oxcarbazepine, phenytoin valproic acid**, and **zonisamide** are supported as initial monotherapy for certain seizure types.
- Some ASMs can worsen certain seizures and should be used cautiously, such as **carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine**, and **vigabatrin** in children with absence or juvenile myoclonic epilepsy.
- ASM therapeutic ranges vary by seizure type. Measuring serum levels helps assess efficacy, adherence, and guide therapy, especially in patients with renal and/or hepatic disease, those taking multiple medications, pregnancy, or oral contraceptive use.
- Older adults often need lower ASM doses due to reduced organ function, drug interactions, central nervous system (CNS) sensitivity, and hypoalbuminemia, which complicates highly bound medications. Body mass changes also affect ASM levels. **Lamotrigine** is often preferred for older patients with focal seizures. Neonates/infants need lower doses, while children may need higher doses than adults.
- **Figure 51-2** shows a suggested algorithm for the treatment of epilepsy.
- ASM monotherapy is preferred. However, more than one ASM may be necessary.
- After 12 months, seizure-free rates are highest for only generalized tonic-clonic seizures (48%–55%), lowest for focal seizures (23%–26%), and

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intermediate for mixed types (25%–32%).

- ASM withdrawal may be considered after over 2 years seizure-free and should always be done gradually.
- About 20%–35% of patients have drug-resistant epilepsy.
- ASM monitoring is shown in **Table 51-2**. Concentration-dependent effects can often be alleviated by decreasing the dose or avoided by slow dose titration.
- Free serum levels, not total, can be measured for highly protein-bound ASMs if altered protein binding is suspected.
- CNS side effects are common and include sedation, dizziness, blurred vision, poor concentration, and ataxia.
- The newer agents have less effect on cognition in general, except **topiramate.**
- All ASMs may raise the risk of suicidal thoughts or behaviors; monitor for worsening depression, suicidal ideation, or mood/behavior changes.
- The most widely recognized idiosyncratic reactions are ASM-induced rashes, which can progress to Stevens–Johnson syndrome/toxic epidermal necrolysis. The HLA-A and B variants may increase risk (see Special Considerations in Patients of Asian and South Asian Descent Section).
- Other reactions include hepatitis and blood dyscrasias. Acute organ failure usually happens within the first 6 months of ASM therapy. Patients with lethargy, vomiting, fever, or rash on ASMs should undergo laboratory tests, including white blood cell count and liver tests.
- Long-term use of certain ASMs (eg, phenytoin, phenobarbital, carbamazepine, valproic acid) can cause osteomalacia or osteoporosis. Chronic therapy patients should undergo vitamin D, calcium, and bone density tests if at risk.
- ASM elimination and liver enzyme effects vary (see **Table 51-3**). Use caution when starting or stopping ASMs, as medication interactions are common.
- Phenobarbital, phenytoin, primidone, and carbamazepine strongly induce metabolism. Valproic acid inhibits metabolism and displaces some drugs from albumin. Felbamate and topiramate can both induce and inhibit metabolism.

TABLE 51-1

Antiseizure Medication Dosing and Target Serum Concentration Ranges

Generic Medication Name (Brand Name)	Initial Total Daily Dose (TTD)	Usual Effective TDD Range	FDA-Recommended Max TDD	Target Serum Concentration Range	Dosing Notes
First Generation					
Carbamazepine (Tegretol, Tegretol XR)	400 mg (>12 yr) 200 mg (6–12 yr) 10–20 mg/kg (<6 yr)	400–1200 mg (>12 yr) 200–1000 mg (6–12 yr) 10–35 mg/kg (<6 yr)	1600 mg (>12 yr) 1000 mg (6–12 yr) 35 mg/kg (<6 yr)	4–12 mcg/mL (mg/L; 17–51 µmol/L)	Doses higher than FDA-recommended max (up to 2400 mg/day) have been used in adults in clinical practice
Clonazepam (Klonopin)	Up to 1.5 mg (≥18 yr) 0.01–0.03 mg/kg (<10	1–8 mg (≥18 yr) 0.01–0.05 mg/kg (<10 yr	20 mg (≥18 yr) 0.05 mg/kg (<10 yr or <30 kg)	20–70 ng/mL (mcg/L; 63–222 nmol/L)	Initial adult TDD may be up to 1.5 mg/day although lower TDD is typically initiated (eg, 0.5–1 mg/day)

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	yr or <30 kg)	or <30 kg)			
Ethosuximide (Zarontin)	500 mg (≥6 yr) 250 mg (3–6 yr)	500–1500 mg (≥6 yr) 20 mg/kg (3–6 yr)	1500 mg (All ages)	40–100 mcg/mL (mg/L; 283–708 µmol/L)	FDA-recommended maximum TDD is not explicitly identified; however, doses ≥1500 mg should only be used with strict monitoring
Phenobarbital (Various)	300 mg (≥18 yr) 5 mg/kg (<18 yr) (15–20 mg/kg LD)	300–600 mg (≥18 yr) 4–8 mg/kg (<18 yr)	600 mg (≥18 yr) 300 mg (<18 yr)	10–40 mcg/mL (mg/L; 43–172 µmol/L)	FDA-recommended doses are not available; however, usual dose ranges and max doses listed here are commonly used in practice
Phenytoin (Dilantin)	300 mg (≥18 yr) 5 mg/kg (<18 yr) (15–20 mg/kg LD)	300–600 mg (≥18 yr) 4–8 mg/kg (<18 yr)	600 mg (≥18 yr) 300 mg (<18 yr)	Total: 10–20 mcg/mL (mg/L; 40–79 µmol/L) Unbound: 0.5–3 mcg/mL (mg/L; 2–12 µmol/L)	Patients >6 yr may require the minimum adult TDD of 300 mg; 600 mg is the maximum recommended TDD in adults; however, higher TDD may be used if serum levels are within therapeutic range
Primidone (Mysoline)	100–125 mg (≥8 yr)	750–1000 mg (≥8 yr)	2000 mg (≥8 yr)	5–10 mcg/mL (mg/L; 23–46 µmol/L)	
Valproic acid, Divalproex, Valproate (Depakene, Depakote DR/ER, Depacon)	10–15 mg/kg (≥10 yr)	20–30 mg/kg (≥10 yr)	60 mg/kg (≥10 yr)	50–100 mcg/mL (mg/L; 347–693 µmol/L)	
Second Generation					
Felbamate (Felbatol)	1200 mg (≥14 yr) 15 mg/kg (2–14 yr)	1200–3600 mg (≥14 yr) 15–45 mg/kg (2–14 yr)	3600 mg (≥14 yr) 45 mg/kg (2–14 yr)	30–60 mcg/mL (mg/L; 126–252 µmol/L)	Pediatric dosing listed is for LGS
Gabapentin (Neurontin)	300–900 mg (≥12 yr) 10–15 mg/kg (3–11 yr)	900–1800 mg (≥12 yr) 25–40 mg/kg (3–11 yr)	3600 mg (≥12 yr) 50 mg/kg (3–11 yr)	2–20 mcg/mL (mg/L; 12–117 µmol/L)	In patients ≥12 yr, TDDs up to 3600 mg/day have been tolerated for short durations; TDDs up to 4800 mg/day are described in the literature
Lamotrigine (Lamictal, Lamictal XR)	25 mg (>12 yr) 0.3 mg/kg (2–12 yr)	225–375 mg (>12 yr) 4.5–7.5 mg/kg (2–12 yr)	500 mg (>12 yr) 300 mg (2–12 yr)	4–20 mcg/mL (mg/L; 16–78 µmol/L)	Dosing recommendations differ if on VPA, CBZ, PB, PHT, PRM, or VPA; refer to PI for specific dose recommendations for patients on those concomitant ASMs
Levetiracetam	1000 mg	2000–3000 mg	3000 mg (≥16 yr)	12–46 mcg/mL (mg/L;	Refer to PI for specific age-based dose

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(Keppra, Keppra XR)	(≥16 yr) 20 mg/kg (6–15 yr) Varies by age (<6 yr)	(≥16 yr) 20–60 mg/kg (6–15 yr) Varies by age (<6 yr)	60 mg/kg (6–15 yr) Varies by age (<6 yr)	70–270 µmol/L)	recommendations for <6 yr; XR formulation is only approved for ages ≥12 yr; an initial TDD of 500 mg can be used for older patients; FDA-approved maximum doses are listed although higher doses are used in clinical practice
Oxcarbazepine (Trileptal, Oxtellar XR)	600 mg (>17 yr) 8–10 mg/kg-max 600 mg (2–16 yr)	1200–2400 mg (>17 yr) 900–1800 mg (2–16 yr)	2400 mg (>17 yr) Varies by age (2–16 yr)	3–35 mcg/mL (MHD) (mg/L; 12–138 µmol/L)	Pediatric dosing listed varies based on weight; refer to PI for specific weight-based dose recommendations; XR formulation is approved for ages 6 and older
Tiagabine (Gabitril)	4 mg if on other ASMs that are inducers and <4 mg if not on inducers (≥12 yr)	32–56 mg if on other ASMs that are inducers and <32–56 mg if not on inducers (≥12 yr)	56 mg if on other ASMs that are inducers and <56 mg if not on inducers (≥12 yr)	0.02–0.2 mcg/mL (mg/L; 0.05–0.5 µmol/L)	Not FDA approved in patients under 12 yr
Topiramate (Topamax, Trokendi XR)	25–50 mg (≥10 yr) 25 mg (2–9 yr)	200–400 mg (≥10 yr) 150–400 mg based on weight (2–9 yr)	400 mg (≥10 yr) Varies based on weight (2–9 yr)	5–20 mcg/mL (mg/L; 15–59 µmol/L)	Pediatric listed dosing varies based on weight; refer to PI for specific weight-based dose recommendations; XR formulation approved for ages 6 and up; maximum recommended TDD is 400 mg; however, up to 1600 mg has been described for specific situations (eg, status epilepticus)
Zonisamide (Zonegran)	100 mg (>16 yr)	200–400 mg (>16 yr)	600 mg (>16 yr)	10–40 mcg/mL (mg/L; 47–188 µmol/L)	FDA-approved pediatric dosing recommendations not available
Third Generation					
Brivaracetam (Briviact)	100 mg (≥16 yr) 50–100 mg if >50 kg or 1–3 mg/kg if <50 kg (1 mo–15 yr)	100–200 mg (≥16 yr) 50–200 mg if >50 kg or 1–6 mg/kg if <50 kg (1 mo–15 yr)	200 mg (≥16 yr) Varies based on weight (1 mo–15 yr)	Not defined	Pediatric dosing listed for patients <50 kg varies based on weight; refer to PI for specific weight-based dose recommendations
Cenobamate (Xcopri)	12.5 mg (≥18 yr)	200–400 mg (≥18 yr)	400 mg (≥18 yr)	Not defined	Not FDA approved in pediatrics
Eslicarbazepine (Aptiom)	400 mg (≥18 yr) 200–400 mg (4–17 yr)	800–1600 mg (≥18 yr) 400–1200 mg (4–17 yr)	1600 mg (≥18 yr) 1200 mg (4–17 yr)	Not defined	Pediatric dosing listed is weight-based; refer to PI for specific weight-based dose recommendations
Lacosamide	100–200 mg	200–400 mg	400 mg (>17 yr)	Not defined	Dosing listed is for focal-onset and generalized-

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(Vimpat)	(>17 yr) 100 mg if >50 kg and 2 mg/kg if <50 kg (4–17 yr)	(>17 yr) 200–400 mg if >50 kg or 4–8 mg/kg if <50 kg (4–17 yr)	400 mg if >50 kg or 8 mg/kg if <50 kg (4–17 yr)		onset tonic-clonic seizures
Perampanel (Fycompa)	2 mg	8–12 mg	12 mg	Not defined	Dosing listed is for patients >4 yr with focal-onset seizures or >12 yr with generalized-onset tonic-clonic seizures
Pregabalin (Lyrica)	150 mg (≥17 yr) 2.5 mg/kg if >30 kg and 3.5 mg/kg between 11 and 29 kg (4–17 yr)	150–600 mg (≥17 yr) 2.5–10 mg/kg if >30 kg and 3.5–14 mg/kg between 11 and 29 kg (4–17 yr)	600 mg (≥17 yr) 600 mg if >30 kg and 14 mg/kg between 11 and 29 kg (4–17 yr)	Not defined	
Third Generation with Indications for Specific Epilepsy Syndromes					
Cannabidiol (Epidiolex)	5 mg/kg (≥2 yr)	10–20 mg/kg (≥2 yr)	20 mg/kg (≥2 yr)	Not defined	Dosing listed is for Dravet syndrome and LGS
Clobazam (Onfi)	5 mg if ≤30 kg and 10 mg if >30 kg (≥2 yr)	5–20 mg if ≤30 kg and 10–40 mg if >30 kg (≥2 yr)	20 mg if <30 kg and 40 mg if >30 kg (≥2 yr)	0.03–0.3 ng/mL (mcg/L; 0.1–1.0 nmol/L)	Dosing listed is for LGS
Everolimus	5 mg/m^2 orally once daily	Adjust dose to attain trough concentration of 5–15 ng/mL (5–15 mcg/L; 5.2–16 nmol/L)		5–15 ng/mL (5–15 mcg/L; 5.2–16 nmol/L); check trough q1–2 weeks after initiation or dose change (see prescribing information for schedule)	Dosing adjusted with following equation: New dose = current dose × (target concentration divided by current concentration)
Fenfluramine (Fintepla)	0.2 mg/kg if not on STP and 0.1 mg/kg if on STP and CLB (≥2 yr)	0.35 mg/kg if not on STP and 0.2 mg/kg/day if on STP and CLB (≥2 yr)	26 mg if not on STP and 17 mg if on STP and CLB (≥2 yr)	Not defined	Dosing listed is for Dravet syndrome
Ganaxolone	18 mg/kg (≤28 kg); 450 mg (>28 kg)	18–63 mg/kg (≤28 kg); 450–1800 (>28 kg)	63 mg/kg (≤28 kg); 1800 (>28 kg)	Not defined	Dose increases weekly based on tolerability; must take with food; see prescribing information for dosing schedule
Rufinamide (Banzel)	400–800 mg (≥17 yr)	1600–3200 mg (≥17 yr)	3200 mg (≥17 yr) 3200 mg (1–16	Not defined	Dosing listed is for LGS; FDA labeling states the efficacy of TDD <3200 mg is unknown; however,

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	10 mg/kg (1–16 yr)	10–45 mg/kg (1–16 yr)	yr)		doses <3200 mg are used in clinical practice
Stiripentol (Diacomit)	50 mg/kg (≥2 yr)	50 mg/kg (≥2 yr)	3000 mg (≥2 yr)	4–22 mg/L (mcg/mL; 17–94 µmol/L)	Dosing listed is for patients with Dravet syndrome who are also on CLB; STP should only be used in combination therapy with CLB
Vigabatrin (Sabril)	1000 mg (≥17 yr) 350–500 mg depending on weight (2–16 yr) 50 mg/kg (infants)	1000–3000 mg (≥17 yr) 1050–2000 mg depending on weight (2–16 yr) 50–150 mg/kg (infants)	3000 mg (≥17 yr) Varies by weight (2–16 yr) 150 mg/kg (infants)	0.8–36 mcg/mL (mg/L; 6–279 µmol/L)	Infant dosing listed is for infantile spasms; adult and noninfant pediatric dosing listed is for refractory focal seizures

CBZ, carbamazepine; CLB, clobazam; DR, delayed-release; ER, extended-release; FDA, Food and Drug Administration; LD, loading dose; LGS, Lennox–Gastaut syndrome; MHD, 10-monohydroxycarbazepine derivative; PB, phenobarbital; PHT, phenytoin; PI, prescribing information; PRM, primidone; STP, stiripentol; TDD, total daily dose; VPA, valproate; XR, extended-release; yr, year(s).

TABLE 51-2

Antiseizure Medications

Mechanism of Action (MOA)/Indication	Advantages/Disadvantages	Interactions	Adverse Medication Effects
First-Generation ASMs			
Carbamazepine (CBZ): IR/ER tablet, chewable tablet, ER capsule, liquid suspension 100 mg/5 mL			
MOA: Enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in comorbid bipolar disorder and trigeminal neuralgia	**Effect of CBZ on ASMs**: Potent CYP3A4, CYP1A2, CYP2B6, CYP2C9/19 inducer; decreases or possibly decreases levels of brivaracetam, clonazepam, eslicarbazepine, ethosuximide, felbamate, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, stiripentol tiagabine, topiramate, valproate, zonisamide	**BOXED WARNING**: Risk of SJS/TEN with HLA-B*1502 allele; aplastic anemia and agranulocytosis **Common**: CNS: diplopia, dizziness, drowsiness; unsteadiness, lethargy; hyponatremia from SIADH
Indication: Monotherapy/adjunctive therapy for focal onset, TC, and mixed seizure types except for absence seizures	**Disadvantages**: Avoid in absence epilepsy due to seizure worsening; screen for SJS/TEN risk (HLA-B*1502 and HLA-A*3101 allele [eg, specific Asian groups]); avoid if prior ASM rash due to possible cross-reaction; 10,11 epoxide metabolite contributes to idiosyncratic adverse effects; avoid with history of bone marrow depression or sensitivity to tricyclic compounds; cannot use	**Effect of ASMs on CBZ**: Cenobamate, eslicarbazepine, felbamate, phenobarbital, phenytoin, primidone, rufinamide may decrease CBZ levels; brivaracetam, felbamate, valproate may increase carbamazepine-10,11 epoxide levels; vigabatrin may increase CBZ	**Serious but rare**: Other blood dyscrasias including thrombocytopenia, leukopenia; DRESS; increased intraocular pressure, cardiovascular: including second and third degree AV heart block; hepatotoxicity;

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	within 14 days of MAO inhibitor; can cause fetal harm	**Others (partial list)**: CYP3A4 inhibitors/inducers may increase/decrease CBZ; CBZ may decrease hormonal contraceptive levels; do not administer with other liquid agents due to the possibility of precipitate occurrence	avoid in porphyria **Long term**: Hyponatremia from SIADH; metabolic bone disease: osteoporosis, osteopenia, osteomalacia
Clonazepam (Schedule IV): Tablet, ODT			
MOA: Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	**Advantages**: Useful when long half-life is needed	**Effect of clonazepam on ASMs**: May affect phenytoin levels	**BOXED WARNING**: Combined with opioids, may cause severe sedation, respiratory depression, coma, or death. **Common**: CNS: sedation and ataxia; behavior problems; paradoxical reactions such as agitation, irritability, aggression, anxiety, anger, nightmares, hallucinations, and psychoses
Indication: Monotherapy/adjunctive therapy for LGS (petit mal variant), akinetic, myoclonic, and absence seizures	**Disadvantages**: May increase TC seizures when used in mixed seizure types; respiratory depression risk with other CNS depressants, including opioids; contraindicated in acute narrow angle glaucoma and severe hepatic impairment; metabolites may accumulate with impaired renal function (adjust dose); some loss of effect may occur after 3 months; withdrawal symptoms including status epilepticus may occur after discontinuation; may increase hypersalivation; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on clonazepam:** Carbamazepine, lamotrigine, phenobarbital, phenytoin may decrease clonazepam levels; vigabatrin increases clonazepam levels; clonazepam may be affected by other enzyme-inducing or enzyme-inhibiting ASMs **Other (partial list)**: Use with opioids, increases the risk of respiratory depression	**Serious but rare**: Respiratory depression; hepatomegaly; muscle weakness **Long term**: Physiologic dependence; hair loss; hirsutism; ankle and facial edema
Ethosuximide (ETX): Capsule, liquid solution 250 mg/5 mL			
MOA: Inhibition of T-type calcium channels	**Advantages**: Medication of choice for absence seizures	**Effect of ETX on ASMs**: May affect carbamazepine, phenobarbital, phenytoin, primidone, valproate	**Common**: GI: nausea/vomiting, cramps, diarrhea; epigastric and abdominal pain; anorexia and weight loss; CNS: lethargy, fatigue, drowsiness, dizziness, ataxia
Indication: Monotherapy and adjunctive therapy for absence seizures in patients ≥3 years of age	**Disadvantages**: May worsen generalized TC seizures and other seizure types when used alone in mixed types of epilepsy; contraindicated with a succinimide allergy; may cause fetal harm; use with caution in hepatic/renal dysfunction	**Effect of ASMs on ETX**: Valproate may increase or decrease ETX levels	**Serious but rare**: Blood dyscrasias: leukopenia, agranulocytosis, pancytopenia, eosinophilia; rash including SJS; DRESS;

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			hepatic/renal dysfunction; lupus erythematosus; CNS: night terrors and paranoid psychosis **Long term**: Behavioral changes
Phenobarbital (PB, Schedule III): Tablet, elixir 20 mg/5 mL, injectable solution, intravenous powder for solution			
MOA: Binds $GABA_A$ receptor nonselectively and potentiates GABA by modulating chloride conductance	**Advantages**: Easily available worldwide; extensive knowledge and experience with PB use despite not being FDA-approved as PB developed in early 1900s prior to the establishment of FDA and current regulatory practices	**Effect of PB on ASMs**: Inducer of CYP1A2, CYP2C9, CYP2C19, CYP3A4. PB may decrease carbamazepine, eslicarbazepine, ethosuximide, felbamate, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, stiripentol, tiagabine, topiramate, valproate, zonisamide	**Common**: CNS: residual sedation or "hangover," impaired cognition, drowsiness, dizziness, vertigo, ataxia, headache, sleep disturbance; paroxysmal effects including excitement, irritability, and hyperactivity in older adults and children; GI: epigastric pain, nausea, vomiting, diarrhea, and constipation
Indication: Oral formulations not FDA-approved but used for focal-onset and generalized seizures; IV powder for solution approved for treatment of neonatal seizures for term and preterm infants	**Disadvantages**: Tolerance and dependence may occur; slow taper when discontinuing after prolonged use; additive CNS effects; may cause respiratory depression; can cause fetal harm; use in neonates requires multi-year monitoring to assess for long-term effects; contraindicated in acute porphyrias	**Effect of ASMs on PB**: Cenobamate, felbamate, rufinamide, and valproate may increase PB levels; phenytoin may increase or decrease PB levels **Other (partial list)**: May decrease levels of oral contraceptives; avoid concomitant use with QT prolonging medications	**Serious but rare**: Respiratory depression and apnea; rash (SJS, TEN); DRESS; cardiac effects including bradycardia, hypotension, and QT prolongation with IV administration, syncope; hepatotoxicity; megaloblastic anemia; apnea and hypoventilation **Long term**: Behavioral changes; connective tissue disorder; intellectual blunting; metabolic bone disease: rickets, osteopenia, osteoporosis, osteomalacia; folate deficiency (with megaloblastic anemia)
Phenytoin (PHT): ER capsule; liquid suspension 125 mg/5 mL; injectable solution; chewable tablet **Fosphenytoin (phenytoin prodrug)**: Injectable solution only			
MOA: Enhances fast inactivation of voltage-gated sodium channels; inhibits persistent sodium current (I_{NAP}) and increases threshold	**Advantages**: May be orally or intravenously loaded in patients who require rapid steady-state serum levels; ER formulation useful in nonadherence as dosed once daily	**Effect of PHT on ASMs**: May decrease brivaracetam, carbamazepine, cenobamate, clonazepam, eslicarbazepine, felbamate, ethosuximide, felbamate, lacosamide, lamotrigine,	**Common: CNS**: Ataxia, nystagmus, slurred speech, decreased coordination, mental confusion, dizziness, insomnia, transient nervousness, headaches

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for action potential firing		oxcarbazepine, perampanel, rufinamide, stiripentol, tiagabine, topiramate, valproate, zonisamide	
Indication: Monotherapy/adjunctive therapy for focal-onset psychomotor seizures and TC seizures; prevention or treatment of seizures during or after neurosurgery, severe TBI, status epilepticus	**Disadvantages**: May aggravate seizures in patients with absence seizures; can increase glucose in diabetes; HLA-B*1502 risk for the development of SJS/TEN in patients of Asian ancestry; CYP2C9*3 carriers may increase development of SCARS; free phenytoin monitoring in renal, hepatic impairment, hypoalbuminemia, and pregnancy; compromised absorption with tube feeds; dose adjustments when switching between free acid and sodium salt formulations; dose adjustments needed in older adults due to decreased clearance; may exacerbate porphyria	**Effect of ASMs on PHT**: Carbamazepine, eslicarbazepine, vigabatrin may decrease PHT levels; brivaracetam, cenobamate, ethosuximide, felbamate, methsuximide, oxcarbazepine, rufinamide, topiramate may increase PHT levels; phenobarbital, valproate may increase or decrease PHT levels **Other (partial list)**: Can substantially reduce delavirdine concentrations and cause loss of virologic response and resistance; may decrease contraceptive levels, may increase/decrease PT/INR when given with warfarin	**Serious but rare**: Blood dyscrasias: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia; lymphadenopathy; rash (SJS/TEN/SCARS); DRESS; hepatotoxicity; angioedema; bradycardia/cardiac arrest; purple glove syndrome with IV administration **Long term**: Connective tissue changes: skin thickening, gingival hyperplasia, coarsening of facial features, enlargement of lips; hirsutism; metabolic bone disease: osteoporosis, osteopenia, osteomalacia; peripheral neuropathy; cerebellar atrophy; folate deficiency (with megaloblastic anemia)
Primidone (PRM): Tablet			
MOA: Prodrug converted to active metabolite phenylethylmalonamide-amide (PEMA) and phenobarbital with the same mechanism of action	**Advantages**: Useful in patients with essential tremor	**Effect of PRM on ASMs**: May decrease carbamazepine, eslicarbazepine, ethosuximide, felbamate, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, stiripentol, tiagabine, topiramate, valproate, zonisamide	**Common**: **CNS**: Ataxia, vertigo, nystagmus, diplopia, drowsiness, fatigue; GI: nausea/vomiting, anorexia, fatigue; emotional: hyperirritability **Serious but rare**: Blood dyscrasias: granulocytopenia, agranulocytosis; rash (SJS, TEN); liver dysfunction
Indication: Monotherapy/adjunctive therapy for focal-onset and TC seizures	**Disadvantages**: Contraindicated in porphyria	**Effect of ASMs on PRM**: may increase PRM; phenytoin may increase or decrease PRM levels; carbamazepine, eslicarbazepine may affect levels	**Long term**: Behavioral changes; intellectual blunting; connective tissue disorder; metabolic bone disease: rickets, osteomalacia; folate deficiency (with megaloblastic anemia)
Valproate (VPA): Divalproex DR sprinkle capsule and tablet, Divalproex ER 24-hour tablet, valproic acid IR capsule and solution 250 mg/5 mL, valproate sodium injectable solution			

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MOA: Multiple mechanisms including inhibition of voltage-dependent sodium and T-type calcium channels, potentiation of GABAergic transmission through enhanced GABA biosynthesis, and inhibition of GABA degradation	**Advantages**: Useful in multiple seizure types, useful in comorbid bipolar disorder and migraine; commonly used in all age groups including ages <10 years	**Effect of VPA on ASMs**: May increase eslicarbazepine, ethosuximide, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, rufinamide, tiagabine, topiramate, zonisamide	**BOXED WARNING**: Hepatotoxicity especially for children <2 years of age and with mitochondrial disorders; fetal risk including neural tube defects, other major malformations, and decreased IQ; pancreatitis including fatal hemorrhagic pancreatitis **Common**: GI: abdominal pain/GI upset (worse with IR), constipation, diarrhea, anorexia, increased appetite, weight gain, nausea/vomiting; CNS: blurred vision, ataxia, dizziness, headache, insomnia, nystagmus, somnolence, abnormal thinking, tremor; dose-dependent thrombocytopenia >100 mg/L (mcg/mL; 693 µmol/L)
Indication: Monotherapy/adjunctive therapy for focal onset and multiple seizure types for patients ≥10 years of age; monotherapy/adjunctive therapy for absence seizures in patients ≥10 years of age	**Disadvantages**: Contraindicated in significant hepatic dysfunction, mitochondrial disorders caused by DNA polymerase γ (POLG) mutations, urea cycle disorders; caution in pancreatitis, and hematopoietic disorders; risk of hyperammonemia with and without encephalopathy with concomitant topiramate use; pregnancy category D—contraindicated in women of childbearing potential and pregnancy category X for pregnant patients treated for migraine prophylaxis	**Effect of ASMs on VPA**: Carbamazepine, phenobarbital, phenytoin, primidone may decrease VPA levels; felbamate may increase VPA levels **Other (partial list)**: Estrogen OC may affect VPA levels	**Serious but rare**: Hyperammonemia with and without encephalopathy; hypothermia with and without hyperammonemia; DRESS; bleeding and other hematopoietic disorders **Long term**: Hair and nail: changes including alopecia, hirsutism, hair texture and color changes, nail and nail bed disorders; irregular menses and polycystic ovary-like syndrome; weight gain; cerebral pseudoatrophy; osteoporosis and osteopenia
Second-Generation ASMs			
Felbamate (FBM): Tablet, liquid suspension 600 mg/5 mL			
MOA: Antagonizes NMDA glutamate receptor; binds weakly to $GABA_A$ receptor and possibly augments GABAergic transmission	**Advantages**: May be useful in refractory epilepsy	**Effect of FBM on ASMs**: May decrease carbamazepine levels; may increase carbamazepine-epoxide, phenobarbital, phenytoin, valproate levels	**BOXED WARNING**: Irreversible fatal aplastic anemia (onset between 5 and 30 weeks and risk greater in females, or history of cytopenia), ASM allergy or

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			significant toxicity, viral infection, and/or immunologic problems (onset between 5 and 30 weeks); acute liver failure with onset in 5 weeks
Indication: Monotherapy/adjunctive therapy for focal-onset seizures with and without TC seizures in patients ≥14 years; adjunctive therapy for focal-onset and generalized seizures associated with LGS in patients aged 2–14	**Disadvantages**: For severe refractory epilepsy ONLY; contraindicated in patients with hepatic dysfunction, history of blood dyscrasias; use with caution in patients with renal dysfunction; available only through special access program; pregnancy category C	**Effect of ASMs on FBM**: Carbamazepine, phenobarbital, phenytoin, and primidone may decrease FBM levels; valproate does not affect FBM levels to a clinically significant degree **Other (partial list)**: Estrogen OC levels not affected	**Common**: GI: anorexia, vomiting, nausea; CNS: insomnia, headache, dizziness, somnolence
Gabapentin (GBP): Tablet, capsule, oral solution 250 mg/5 mL			
MOA: Binds to presynaptic $\alpha_2\delta$ subunit of calcium channels with unknown antiseizure effect	**Advantages**: Useful in postherpetic neuralgia, chronic pain, and neuropathy; few interactions	**Effect of GBP on ASMs**: No significant effect	**Common**: CNS: somnolence, dizziness, ataxia, fatigue, nystagmus; peripheral edema and weight gain; GI: nausea/vomiting
Indication: Adjunctive therapy for focal-onset seizures with and without TC seizures in patients ≥3 years	**Disadvantages**: Considered weakly efficacious; potential misuse with opioids; withdrawal reaction with anxiety, insomnia, nausea, sweating, and increased pain; absorption may be impaired for single oral doses >1200 mg; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on GBP**: No significant effects	**Serious but rare**: Anaphylaxis, angioedema, DRESS; neuropsychiatric symptoms in children 3–12 years of age **Long term**: Weight gain, peripheral edema
Lamotrigine (LTG): Tablet, chewable tablet,[a] ODT,[a] XR tablet[a]			
MOA: Enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in bipolar disease; XR useful in nonadherence as dosed once daily	**Effect of LTG on ASMs**: No significant effects	**BOXED WARNING**: Rash including SJS, TEN with increased risk if given with valproate, exceeding recommended initial dose or dose escalation
Indication: Adjunctive therapy in focal-onset and TC seizures, generalized seizures of LGS in patients ≥2 years of age; monotherapy in patients with focal-onset seizures ≥16 years of age	**Disadvantages**: Slow titration required to avoid rash including SJS; more likely if prior ASM rash and concomitant use of valproic acid; rash incidence higher in children; may exacerbate myoclonus; may have cardiac effects and avoid in 2° and 3° heart block and arrhythmias; dosage adjustment required in patients with moderate and severe liver impairment; no adequate data in	**Effect of ASMs on LTG**: Carbamazepine, cenobamate, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide may decrease LTG levels; cannabidiol increases LTG and valproate increases LTG levels by 2× **Other (partial list)**: Estrogen OCs	**Common**: CNS: dizziness, headache, diplopia, ataxia, blurred vision, somnolence, tremor; GI: including nausea/vomiting, abdominal pain, diarrhea; other effects: rhinitis, pharyngitis, infection, fever; rash

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	pregnancy—may cause fetal harm	may decrease LTG by 50%	**Serious but rare**: DRESS; blood dyscrasias; hemophagocytic lymphohistiocytosis (HLH); SJS/TEN rash (usually after 3–4 weeks and is typically generalized, erythematous, and morbilliform but can progress to SJS)
Levetiracetam (LEV): Tablet, XR tablet,[a] oral solution 500 mg/5 mL, oral tablet of suspension, injectable solution			
MOA: Binds to and selectively inhibits synaptic vesicle $SV2_A$ protein, thereby preventing neurotransmitter release	**Advantages**: Minimal interactions; XR useful as dosed once daily	**Effect of LEV on ASMs**: No significant effects	**Common**: CNS: somnolence, fatigue; behavior effects including aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional liability, hostility, irritability
Indication: Monotherapy/ adjunctive therapy for focal-onset seizures in patients >1 month; adjunctive therapy for myoclonic seizures in patients with JME ≥12 years of age, and generalized TC seizures in patients ≥6 years of age with generalized epilepsy	**Disadvantages**: May worsen depression, PTSD, anxiety, thought disorders; must dose adjust in dialysis/renal failure; pregnancy category C	**Effect of ASMs on LEV**: No significant effects	**Serious but rare**: Psychosis (especially in children), hallucinations; DRESS
Oxcarbazepine (OXC): Tablet, tablet ER,[a] liquid suspension 300 mg/5 mL[a]			
MOA: Enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in bipolar disorder; ER useful in nonadherence as dosed once daily	**Effects of OXC on ASMs**: inhibitor of CYP2C19 and inducer of CYP3A4/5; OXC may decrease lamotrigine levels through UGT induction and decrease perampanel levels; OXC may increase phenytoin levels	**Common**: CNS: dizziness, somnolence, diplopia, fatigue, ataxia, abnormal vision, headache, nystagmus, tremor; GI: including nausea, vomiting; hyponatremia due to SIADH; rash
Indication: Monotherapy/adjunctive therapy for focal-onset seizures in patients ≥4 years of age; adjunctive therapy for focal-onset seizures in patients ≥2 years of age	**Disadvantages**: Higher incidence of hyponatremia, (as high as 25%); HLA-B*1502 in Asians may increase SJS or TEN risk; may require slower titration in renal impairment; active MHD metabolite may decrease in pregnancy; no adequate data in pregnant patients—may cause fetal harm	**Effect of ASMs on OXC**: Carbamazepine, phenobarbital, phenytoin, primidone may decrease levels of OXC active metabolites; valproate may increase levels of OXC **Other (partial list)**: OXC may decrease estrogen OC levels	**Serious but rare**: SJS, TEN; DRESS; blood dyscrasias

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Tiagabine (TGB): Tablet			
MOA: Inhibitor of GABA reuptake transporter GAT1	**Advantages**: None noted	**Effect of TGB on ASMs**: May decrease VPA levels by 10%	**Common**: CNS: dizziness, lightheadedness, somnolence, abnormal thinking; behavior effects including asthenia, lack of energy, nervousness, irritability, difficulty with concentration or attention; GI: abdominal pain, nausea, and vomiting
Indication: Adjunctive therapy for focal-onset seizures in patients ≥12 years of age	**Disadvantages**: Associated with new-onset seizure, status epilepticus, and exacerbation of EEG abnormalities in those with existing epilepsy; dosage reduction may be necessary in patients with liver disease; pregnancy category C	**Effects of ASMs on TGB**: Carbamazepine, phenobarbital, phenytoin, and primidone increase TGB clearance by 60% and may decrease TGB levels; valproate may increase TGB levels by 40%	**Serious but rare**: Increase in generalized seizures and nonconvulsive SE in patients with refractory epilepsy; occurrence of seizures and SE in patients without epilepsy; moderately severe to incapacitating generalized weakness; exacerbation of EEG abnormalities; rash including SJS **Long term**: Possibility of long-term ophthalmologic effects
Topiramate (TPM): Sprinkle capsule, tablet, ER capsule, liquid solution 125 mg/5 mL			
MOA: Antagonizes voltage-gated sodium channel; binds to $GABA_A$ receptor and augments GABAergic transmission, antagonizes AMPA/kainate glutamate receptor, weak carbonic anhydrase inhibitor	**Advantages**: Useful in comorbid migraine and obesity; ER useful in nonadherence as dosed once daily	**Effect of TPM on ASMs**: Is weak inhibitor of CYP2C19 and inducer of CYP3A4; may increase or decrease ASMs metabolized by CYP2C19 and 3A4 including felbamate and topiramate	**Common**: CNS: fatigue, difficulty concentrating, confusion, language problems, tremor, paresthesias; behavioral effects including nervousness, anxiety
Indication: Monotherapy/adjunctive therapy for focal-onset seizures or primary generalized TC seizures in patients ≥2 years of age; adjunctive therapy for patients with LGS ≥2 years of age	**Disadvantages**: Avoid in patients with preexisting cognitive issues; renally dose adjust with CrCl <70 mL/min (1.17 mL/s); can cause fetal harm	**Effect of ASMs on TPM**: Carbamazepine, phenobarbital, phenytoin, and primidone may decrease TPM levels; valproate may increase TPM levels **Other (partial list)**: TPM at higher doses may decrease estrogen OC levels	**Serious but rare**: Renal stones, ophthalmologic conditions: acute myopia and glaucoma; with VPA use: hypo/hyperthermia, oligohidrosis, metabolic acidosis, SJS, TEN, and hyperammonemia with and without encephalopathy

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			Long term: Weight loss; renal stones; metabolic acidosis
Zonisamide (ZON): Capsule, oral suspension 100 mg/5 mL			
MOA: Enhances fast inactivation of voltage-gated sodium channels; inhibits T-type calcium channels; weak carbonic anhydrase inhibitor	**Advantages**: Useful in tremor; useful in nonadherence as dosed once daily	**Effect of ZON on ASMs**: No significant DDIs	**Common**: CNS: sedation, ataxia, confusion, depression, difficulty concentrating, word-finding difficulties
Indication: Adjunctive therapy for focal-onset seizures in patients >16 years	**Disadvantages**: Contraindicated in those with sulfa allergy; dose efficacy may plateau at 400 mg; should not be used in renal failure due to increases in SCr and BUN and possible effects on GFR; pregnancy category C	**Effect of ASMs on ZON**: CYP3A4 inhibitors or inducers may alter ZON levels; carbamazepine, phenobarbital, phenytoin, and valproate may decrease ZON levels	**Serious but rare**: Oligohidrosis and hyperthermia; renal stones; metabolic acidosis; rash (SJS, TEN); DRESS; fulminant hepatic necrosis; blood dyscrasias **Long term**: Weight loss; renal stones; metabolic acidosis
Third-Generation ASMs			
Brivaracetam (BRV, Schedule V): Tablet, oral solution, injectable solution			
MOA: Binds to and selectively inhibits synaptic vesicle $SV2_A$ protein thereby preventing neurotransmitter release	**Advantages**: Can consider converting well-controlled patients from levetiracetam if intolerable psychiatric adverse effects	**Effect of BRV on ASMs**: May increase carbamazepine metabolite; BRV may increase phenytoin levels; no added therapeutic benefit when given with levetiracetam	**Common**: CNS: sedation, fatigue, ataxia, nystagmus; behavioral effects including irritability, aggressive behavior, anxiety, agitation, restlessness, tearfulness, apathy, altered mood, mood swings, hyperactivity, adjustment disorder; GI: nausea, vomiting
Indication: Monotherapy/adjunctive therapy for focal-onset seizures in patients ≥1 month of age; injection solution approved for ≥16 years of age	**Disadvantages**: Dosage adjustments required in hepatic impairment; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on BRV**: CYP2C19 inhibitors may alter BRV levels **Other (partial list)**: Rifampin will reduce BRV levels	**Serious but rare**: Angioedema; bronchospasm; decreased neutrophils; psychosis and depression; hematologic abnormalities including leukopenia and neutropenia
Cenobamate (CBM, Schedule V): Tablet			
MOA: Inhibition of voltage-gated sodium channels; positive	**Advantages**: None	**Effect of CBM on ASMs**: CYP2C19, CYP2B6, CYP3A inhibitor and may increase substrate levels; CY2B6,	**Common**: CNS: somnolence, dizziness, fatigue, diplopia, headache; dizziness and

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allosteric modulator of $GABA_A$ ion channel		CYPC8, CYP3A4 inducer and may decrease substrate levels; may increase phenytoin, phenobarbital, clobazam concentrations; may decrease lamotrigine, carbamazepine concentrations; does not affect valproic acid, levetiracetam, or lacosamide	disturbance in gait and coordination; cognitive dysfunction: memory impairment, disturbance in attention, confusional state, slowness of thought; vision: diplopia, blurred vision, and impaired vision; laboratory: elevated hepatic transaminases, and potassium
Indication: Monotherapy/adjunctive therapy for focal-onset seizures in adults	**Disadvantages**: Must be slowly titrated q2 weeks to avoid DRESS; contraindicated in Familial Short QT syndrome; caution when administering with other medications that shorten QT interval; use with caution and dose reduce in hepatic and renal impairment; use not recommended in end-stage hepatic or renal disease; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on CBM**: Phenytoin may decrease CBM; valproate, phenobarbital, carbamazepine do not significantly impact CBM **Other (partial list)**: CBM may decrease estrogen OC levels; additive risk with other medications that shorten the QT interval; use with CNS depressants increases CNS toxicity	**Serious but rare**: DRESS with fast titration (weekly intervals); QT interval shortening; appendicitis
Eslicarbazepine (ESL): Tablet			
MOA: Selectively enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in nonadherence as dosed once daily	**Effect of ESL on ASMs**: Inhibitor of CYP2C19; may affect carbamazepine, perampanel, phenytoin, phenobarbital, primidone levels	**Common**: CNS: dizziness, somnolence, nausea, headache, diplopia, fatigue, vertigo, ataxia, blurred vision, tremor; hyponatremia due to SIADH; rash
Indication: Monotherapy or adjunctive therapy for focal-onset seizures in patients ≥4 years of age	**Disadvantages**: Avoid in severe hepatic impairment; dose adjustment in renal failure; avoid concomitant use with carbamazepine and oxcarbazepine; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on ESL**: Carbamazepine, phenobarbital, primidone, and phenytoin may decrease ESL levels **Other (partial list)**: ESL decreases estrogen OC levels	**Serious but rare**: SJS; anaphylaxis, angioedema, DRESS; cardiac effects including prolonged PR interval, AV block; hepatotoxicity; blood dyscrasias **Long term**: Hyponatremia
Lacosamide (LCM, Schedule V): Tablet, ER tablet, oral solution, injectable solution			
MOA: Selectively enhances slow inactivation of voltage-gated sodium channels	**Advantages**: Minimal interactions	**Effect of LCM on ASMs**: Potential CYP2C19 inhibitor but no clinically significant effects on other ASMs have been observed	**Common**: CNS: diplopia, headache, nausea, somnolence, dizziness, ataxia; GI: constipation, diarrhea, nausea, vomiting, dyspepsia, dry mouth, oral hypoesthesia/paresthesia; laboratory: LFT elevations

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Indication: Monotherapy/adjunctive therapy for focal-onset seizures in patients ≥4 years of age; adjunctive therapy for primary generalized TC seizures in patients ≥4 years of age	**Effect of ASMs on LCM**: LCM is a substrate of CYP3A4, CYP2C9, and CYP2C19; carbamazepine, phenytoin, phenobarbital, primidone may decrease LCM levels by 15%–20% **Other (partial list)**: LCM may increase levels of strong CYP3A4 or CYP2C9 inhibitors in renal or hepatically impaired patients; risk of cardiac abnormalities increased with concomitant medications that affect cardiac conduction	**Disadvantages**: Avoid in third-degree heart block; must obtain ECG prior to intravenous infusion; use cautiously with underlying proarrhythmic conditions or on medications that affect cardiac conduction; not recommended in severe hepatic impairment; requires dose adjustment in renal impairment; oral solution contains phenylalanine and is a risk in patients with phenylketonuria no adequate data in pregnancy—may cause fetal harm	**Serious but rare**: Cardiac: AV conduction abnormalities, prolonged PR interval, atrial arrhythmias, syncope (especially in patients with diabetes); DRESS and hypersensitivity effects; blood abnormalities: neutropenia and anemia
Perampanel (PER, Schedule III): Tablet, oral suspension			
MOA: Selectively and noncompetitively antagonizes AMPA glutamate receptor on postsynaptic neuron	**Advantages**: Useful in mixed seizure types; useful in nonadherence as dosed once daily	**Effect of PER on ASMs**: Modest enzyme inducer at high doses	**BOXED WARNING**: Aggression, hostility, irritability, anger, and homicidal ideation
Indication: Monotherapy for focal-onset seizures in patients ≥4 years of age; adjunctive therapy for primary generalized TC seizures in patients ≥12 years of age	**Disadvantages**: Avoid in active psychosis, significant hostility or aggressive behavior; avoid in severe hepatic/renal impairment or hemodialysis; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on PER**: Carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate decrease PER levels; valproate has no effect on PER levels **Other (partial list)**: PER decreases estrogen OC levels	**Common**: CNS: dizziness, somnolence, fatigue, falls, vertigo, ataxia, headache, confusion; GI: nausea, weight gain, vomiting, abdominal pain; behavioral: irritability anxiety; weight gain; falls sometimes leading to serious head injuries **Serious but rare**: DRESS
Pregabalin (PGB, Schedule V): Capsule, tablet CR, oral solution			
MOA: Binds to presynaptic $\alpha_2\delta$ subunit of calcium channels	**Advantages**: Useful in patients with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, neuropathic pain with spinal cord injury; minimal DDIs due to renal excretion	**Effect of PGB on ASMs**: No significant effects	**Common**: CNS: dizziness, somnolence, blurred vision, difficulty with concentration and attention; dry mouth; edema and weight gain
Indication: Adjunctive therapy for focal-onset seizures in patients ≥4 years of age	**Disadvantages**: Caution in preexisting cognitive disorders; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on PGB**: No significant effects	**Serious**: Potential for misuse when taken with opiates **Long term**: Weight gain
Third-Generation ASMs with FDA Approval for Specific Epilepsy Syndrome Indications			
Cannabidiol (CBD, Schedule V): Oral solution			

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MOA: Unknown, does not act on cannabinoid receptors	**Advantages**: Useful for refractory seizures in LGS and Dravet syndrome	**Effect of CBD on ASMs**: Increases lamotrigine; increases and clobazam active metabolite by 3×	**Common**: CNS: somnolence, fatigue, malaise, asthenia; sleep disorders including insomnia, poor quality sleep; GI: decreased appetite; diarrhea; transaminase elevations
Indication: Monotherapy/adjunctive therapy for patients with LGS, TSC, and Dravet syndrome, ≥2 years of age	**Disadvantages**: Avoid if hypersensitivity reactions to cannabis, THC; liver function and bilirubin monitoring before and at 1, 3, and 6 months of treatment specially if given with valproate; no adequate data in pregnant woman—may cause fetal harm	**Effect of ASMs on CBD**: CYP3A4 and CYP2C19 inhibitors will increase CBD levels; CYP3A4 and CYP2C19 inducers will decrease CBD levels	**Serious but rare**: Hepatotoxicity; hypoxia; respiratory failure
Clobazam (CLB, Schedule IV): Tablet, oral suspension			
MOA: Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	**Advantages**: Despite FDA approval for LGS only, may be useful in all types of epilepsy; less sedating benzodiazepine	**Effect of CLB on ASMs**: Inhibitor of CYP2C9 and inducer of CYP3A4; CLB may affect levels of CYP2C9, CYP3A4 substrates	**BOXED WARNING**: Concomitant use with opioids increases risk of death **Common**: CNS effects including somnolence, sedation, lethargy; pyrexia; constipation; drooling
Indication: Adjunctive therapy for patients with LGS ≥2 years of age	**Disadvantages**: Monitor patients with history of substance use; use with other CNS depressants may produce additive CNS effects; may cause respiratory depression, coma, and death; no adequate data in pregnant patients—may cause fetal harm	**Effect of ASMs on CLB**: Carbamazepine, felbamate, phenobarbital, phenytoin, primidone may decrease CLB levels; cannabidiol, cenobamate, stiripentol increase CLB levels **Other (partial list)**: CLB decreases estrogen OC levels	**Rare but serious**: Rash (SJS, TEN); anemia; liver enzyme elevations; respiratory depression
Everolimus (EVL): Tablets for suspension			
MOA: Inhibition of mTOR	**Advantages**: Useful for refractory seizures in TSC	**Effect of EVL on ASMs**: Increases CBZ, CLB, and OXC levels ~10%	**Common**: GI: stomatitis (>30%), diarrhea, vomiting; hematologic: neutropenia, anemia, thrombocytopenia; metabolic: hypercholesterolemia; hypertriglyceridemia; pyrexia; cough; rash; elevated AST/ALT, hyperphosphatemia
Indication: Adjunctive treatment of focal seizures associated with TSC in patients ≥2 years	**Disadvantages**: Numerous ADEs that occur commonly and at Grade 3/4 severity; close monitoring necessary including CBC, glucose, lipid profile, and renal function; withhold for at	**Effect of ASMs on EVL**: Pgp and strong CYP3A4 inhibitors CBD can increase EVL levels (monitor levels)	**BOXED WARNING**: Stomatitis; noninfectious pneumonitis; bacterial, fungal, viral, and protozoal infections

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of age	least 1 week before elective surgery due to impaired wound healing; avoid live vaccines; can cause fetal harm; secreted into breast milk		including opportunistic infections (avoid live vaccines); myelosuppression; metabolic disorders **Less common**: Hypersensitivity reactions, increased angioedema risk with ACE inhibitors, renal failure **Other**: Impaired wound healing, radiation sensitization and radiation, embryofetal toxicity, menstrual irregularities, may impair fertility in males and females
Fenfluramine (FEN): Oral solution			
MOA: Increases extracellular serotonin through actions on serotonin transporter protein, agonist at serotonin 5-HT_2 receptors	**Advantages**: Useful for refractory seizures in Dravet syndrome	**Effect of FEN on ASMs**: No significant effects	**BOXED WARNING**: Risk of valvular heart disease and pulmonary arterial hypertension; echocardiograms required before, during, and after treatment
Indication: Treatment of seizures associated with LGS and Dravet syndrome in patients ≥2 of age	**Disadvantages**: Contraindicated within 14 days of MAO inhibitors due to risk of serotonin syndrome; may increase blood pressure; not recommended in severe hepatic or renal impairment; available only through FINETPLA REMS; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on FEN**: CYP1A2, 2B6 inducers will decrease FEN; stiripentol + clobazam will increase FEN concentrations (max daily dose of FEN is reduced to 17 mg); cyproheptadine and potent 5-HT serotonin receptor binding agents may decrease efficacy of FEN **Other (partial list)**: Rifampin will decrease FEN, strong CYP1A2 and CYP2B6 inducers will decrease FEN	**Common**: GI: decreased appetite/weight, vomiting, diarrhea, constipation; CNS: somnolence, sedation, lethargy; fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increase; salivary effects like drooling, hypersecretion; pyrexia; falls; status epilepticus; abnormal echocardiogram **Rare but serious**: Increased blood pressure including hypertensive crisis; risk of valvular disease and pulmonary arterial hypertension; mydriasis precipitating acute angle closure glaucoma
Ganaxolone (GNX, Schedule V): Oral suspension (50 mg/mL)			
MOA: Neuroactive steroid	**Advantages**: Useful for seizures in CDKL5;	**Effect of GNX on ASMs**: None	**Common**: CNS: somnolence

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that is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptor	different from benzodiazepines and other GABAergic ASMs, modulates extrasynaptic as well as synaptic $GABA_A$ receptors; may have beneficial effects on mood, anxiety		and sedation (may be potentiated by CNS depressants); pyrexia; salivary hypersecretion; seasonal allergy
Indication: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder in patients ≥2 years of age	**Disadvantages**: Dose reduction required in hepatic impairment; no adequate data in pregnancy; secreted in human milk	**Effect of ASMs on GNX**: Strong or moderate CYP3A4 inducers (CBZ, PHT, PB, and PRM) reduce GNX level	**Rare but serious**: None
Rufinamide (RFN): Tablet, oral suspension			
MOA: Selectively enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful for refractory seizures in LGS	**Effect of RFN on ASMs**: Weak inhibitor of CYP2E1 and weak inducer of CYP3A4; modestly decreases levels of carbamazepine, lamotrigine; increases levels of phenobarbital, phenytoin	**Common**: CNS: somnolence, fatigue, coordination abnormalities, dizziness, gait disturbances, ataxia; GI: nausea
Indication: Adjunctive therapy for patients with LGS ≥1 year of age	**Disadvantages**: Contraindicated in severe liver impairment or in familial short QT syndrome; use caution with other drugs that shorten QT interval; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on RFN**: Carbamazepine, phenobarbital, phenytoin decrease RFN levels by 19%–46%; valproate increases RFN levels up to 70% **Other (partial list)**: RFN decreases estrogen OC levels	**Rare but serious**: DRESS; rash (SJS); status epilepticus; leukopenia; QT interval shortening
Stiripentol (STP): Capsule			
MOA: Possibly acts on $GABA_A$ receptor and may also inhibit CYP450 to increase blood levels of clobazam and its active metabolite	**Advantages**: Useful for refractory seizures in Dravet syndrome	**Effect of STP on ASMs**: Inhibitor and inducer of CYP1A2, 2B6, 3A4 and possible inhibitor of CYP2C8, 2C19, Pgp transporter, BCRP transporter; STP increases clobazam concentration twofold and clobazam active metabolite fivefold (must decrease clobazam when used together)	**Common**: Somnolence, decreased appetite/weight, agitation, ataxia, hypotonia, nausea, tremor, dysarthria, insomnia
Indication: Adjunctive therapy with clobazam for seizures associated with Dravet syndrome in patients ≥2 (no evidence for monotherapy)	**Disadvantages**: Must be adjunctively with clobazam; hematologic testing required prior to first dose and q6 months due to neutropenia and thrombocytopenia risk; powder formulation contains phenylalanine—risk in patients with phenylketonuria; not recommended in moderate or severe hepatic or renal impairment; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on STP**: STP is substrate of CYP1A2, CYP2C19, CYP3A4 and phenytoin, phenobarbital, carbamazepine may decrease stiripentol levels	**Serious but rare**: Neutropenia and thrombocytopenia; monitor

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Vigabatrin (VGB): Tablet, powder packet			
MOA: Binds to and irreversibly inhibits GABA transaminase	**Advantages**: Useful in infantile spasms for whom the potential benefit outweighs risk of vision loss; renally cleared and has less DDIs than other ASMs	**Effect of VGB on ASMs**: Inducer of CYP2C9; decreases levels of phenytoin by 20%; possibly increases levels of carbamazepine by 10%; increases C_{max} of clonazepam	**BOXED WARNING**: Progressive and permanent bilateral peripheral visual loss including tunnel vision and decrease in visual acuity **Common**: CNS: fatigue, somnolence, nystagmus, tremor, blurred vision, vision loss, memory impairment, abnormal coordination, confusion; weight gain; edema; peripheral neuropathy; laboratory abnormalities: decreases in ALT/AST in pediatric patients; aggression; Infection: upper respiratory tract infection, bronchitis, ear infection, and acute otitis media
Indication: Adjunctive therapy for refractory focal-onset seizures in patients ≥2 years of age (not indicated as first-line); monotherapy for infantile spasms in patients 1 month to 2 years of age	**Disadvantages**: Permanent vision loss in most patients after a certain duration of exposure, requiring eye exams Q3 months; requires REMS program registration; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on VGB**: Carbamazepine, primidone, and valproate have no effect on VGB **Other (partial list)**: Unlikely to affect estrogen OC levels	**Serious but rare**: Seizure exacerbation, particularly absence and myoclonic seizures in generalized epilepsies; anemia; vision loss is unpredictable with risk increasing in a dose-related and life exposure–related manner; abnormal MRI signal changes in infants treated for infantile spasms strongly suggestive of intramyelinic edema in select brain areas

AMPA, A-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASM, antiseizure medication; AV, atrioventricular; BCRP, breast cancer resistance protein; BUN, blood urea nitrogen; C_{max}, maximum concentration; CNS, central nervous system; CR, controlled-release; CrCl, creatinine clearance; CYP, cytochrome p450 isoenzyme system; DDI, drug-drug interaction; DR, delayed-release; DRESS, drug rash with eosinophilia and systemic symptoms; EEG, electroencephalogram; FDA, Food and Drug Administration; ER, extended-release; GABA, gamma-aminobutyric acid; GAT1, GABA transporter type 1; GFR, glomerular filtration rate; GI, gastrointestinal; HLA, human leukocyte antigen; IQ, intelligence quotient; IR, immediate release; IV, intravenous; LGS, Lennox–Gastaut syndrome; MAO, monoamine oxidase; mTOR, mammalian target of rapamycin; OCs, oral contraceptives; ODT, orally dissolving tablet; PT/INR, prothrombin time/international normalized ratio; PTSD, posttraumatic stress disorder; REMS, Risk Evaluation and Mitigation Strategy; SCARS, severe cutaneous adverse reactions; SIADH, Syndrome of Inappropriate Antidiuretic Hormone Secretion; SJS, Steven–Johnson syndrome; TBI, traumatic brain injury; TC, tonic-clonic; TEN, toxic epidermal necrolysis; TSC, tuberous sclerosis; UGT, UDP-glucuronosyltransferase; XR, extended-release.

[a]All ASMs may increase the risk of suicidal thoughts or behavior and patients treated with an ASM should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

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TABLE 51-3

Antiseizure Medication Elimination Pathways and Major Effects on Hepatic Enzymes

Antiepileptic Medications	Major Hepatic Enzymes	Renal Elimination (%)	Induces	Inhibits
First Generation				
Carbamazepine	CYP3A4	3	CYP1A2; CYP2B6; CYP2C9/19; CYP3A; GT	None
Clonazepam	CYP3A	2	None	None
Ethosuximide	CYP3A4; CYP2E1	10–20	None	None
Phenobarbital	CYP2C9; CYP2C19	25	CYP 3A4/2C9/2C19/1A2; GT	None
Phenytoin	CYP2C9; CYP2C19	Unknown	CYP3A; CYP2C; GT	
Primidone		<1		
Valproate	GT; β-oxidation	<3	None	CYP2C9; GT epoxide hydrolase
Second Generation				
Felbamate	CYP3A4; CYP2E1; other	50	CYP3A4	CYP2C19; β-oxidation
Gabapentin	None	Almost completely	None	None
Lamotrigine	GT	10	GT	None
Levetiracetam	None (undergoes nonhepatic hydrolysis)	66	None	None
Oxcarbazepine (MHD is the active metabolite.)	Cytosolic system	<1 (27 as MHD)	CYP3A4; CYP3A5; GT	CYP2C19
Tiagabine	CYP3A4; CYP1A2; CYP2D6; CYP2C19	2	None	None
Topiramate	Not known	70	CYP3A (dose dependent)	CYP2C19
Zonisamide	CYP3A4	35	None	None
Third Generation				
Brivaracetam	CYP2C19	<10	None	CYP2C19 (weak), GT epoxide hydrolase

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Cenobamate	UGT2B7/B4; CYP2E1; CYP2A6; CYP2B6; CYP2C19; CYP3A4/5	6.4	CYP2B6; CYP2C8; CYP3A4	CYP 2B6; CYP2C19; CYP3A
Eslicarbazepine	Undergoes hydrolysis	67	GT (mild)	CYP2C19
Lacosamide	CYP2C9/19; CYP3A4	40	None	CYP2C19
Perampanel	CYP3A4/5; CYP1A2; CYP2B6	Undefined	CYP3A4/5; CYP2B6; GT	CYPA3A4/5; CYP2C8; GT
Pregabalin	None	100	None	None
Third Generation with Indications for Specific Epilepsy Syndromes				
Cannabidiol	CYP2C19; CYP3A4; GT	Minor	CYP1A2; CYP2B6; GT	CYP2C8/9/19
Clobazam	CYP3A4; CYP2C19; CYP2B6	2	CYP3A4 (weak)	CYP2C9
Everolimus	CYP3A4	None	Unknown; not tested with doses used for epilepsy	Unknown; not tested doses used for epilepsy
Fenfluramine	CYP1A2; CYP2B6; CYP2D6	<25	None	None
Ganaxolone	CYP3A4/5; CYP2B6; CYP2C19; CYP2D6	None	None	None
Rufinamide	Hydrolysis	2	CYP3A4 (weak)	CYP2E1 (weak)
Stiripentol	CYP1A2; CYP2C19; CYP3A4	0.1	CYP1A2; CYP2B6; CYP3A4	CYP1A2; CYP2B6; CYP3A4; CYP 2C8/19
Vigabatrin	None	Almost completely	CYP2C9	None

CYP, cytochrome P450 isoenzyme system; GT, glucuronyltransferase; MHD, monohydroxy derivative, 10-OH-carbazepine.

FIGURE 51-2

An algorithm for ASM therapy. ASM, antiseizure medication; VNS, vagal nerve stimulation; QOL, quality of life.

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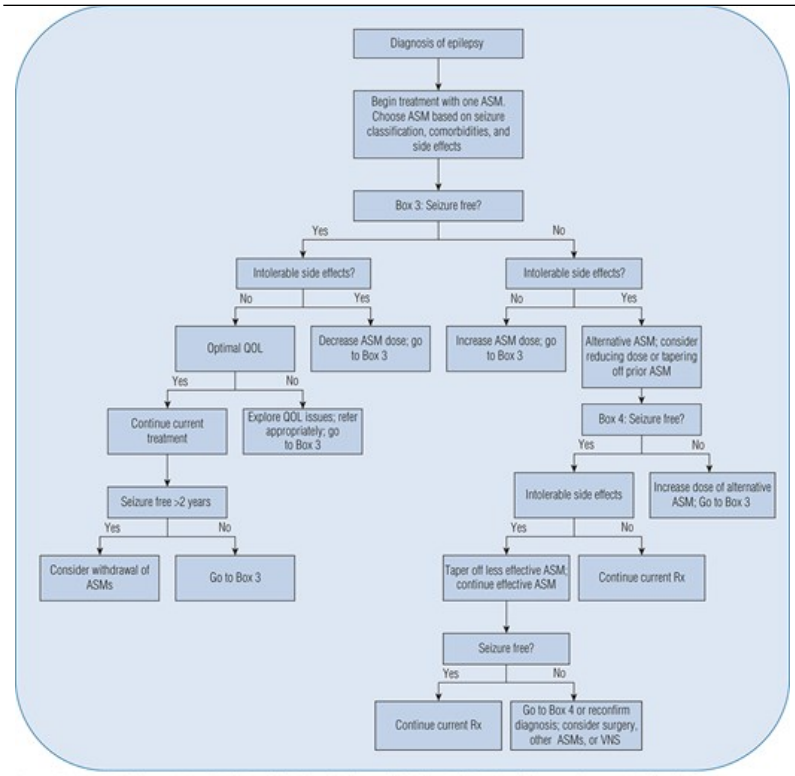

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Special Considerations in Patients of Reproductive Age

- Seizures harm both pregnant patients and fetuses.
- Estrogen slightly increases, and progesterone slightly decreases seizure risk. Enzyme-inducing ASMs (like phenytoin, carbamazepine, topiramate) may reduce contraceptive effectiveness; use backup birth control and twice the usual dose of emergency contraception.
- For catamenial epilepsy (seizures just before or during menses) or seizures that occur during ovulation, try standard ASMs first; consider intermittent high-dose ASMs, benzodiazepines, or progestational agents if needed. Acetazolamide has limited success. Seizures often improve in frequency at menopause.
- Individuals with epilepsy who are seizure-free for 9–12 months before pregnancy have an 84%–92% chance of remaining seizure-free during pregnancy. ASM levels may change due to pregnancy-related physiological shifts.
- ASMs in pregnancy can increase risks for major congenital malformations (MCMs), neurodevelopmental outcomes (eg, intellectual disability, autism spectrum disorder [ASD]), and growth restrictions. Risk varies by ASM. General MCM prevalence is 2.4%–2.9%; patients should know how ASMs may raise this risk.
- Choosing an effective single ASM before conception is crucial. Teratogenic risks must be considered for reproductive-age patients, as unplanned pregnancies and early MCMs are common.
- Valproic acid has the highest risk of MCMs (~10%), neural tube defects, other malformations, and neurodevelopmental issues, so it should be avoided in pregnancy.
- Phenobarbital is linked to cardiac defects and oral clefts and should be avoided.
- Topiramate increases the risk of small gestational age, oral clefts, and may raise chances of intellectual disability, ASD, and attention deficit hyperactivity disorder.

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- ASM monotherapy is preferred in pregnancy. Lamotrigine, levetiracetam, and oxcarbazepine are recommended when suitable for seizure type and patient factors.
- If an ASM controls generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures, use caution before stopping or switching, even if it is not ideal for fetal outcomes.
- ASM levels may fluctuate in pregnancy due to reduced gastric motility, nausea, increased distribution, renal elimination, altered liver enzymes, and protein binding changes.
- ASM level changes during pregnancy are greatest with lamotrigine, levetiracetam, oxcarbazepine, zonisamide, and topiramate; some reports also suggest changes with phenobarbital, valproic acid, primidone, and ethosuximide.
- Adequate folic acid may help prevent teratogenic effects. All women of childbearing age should take at least 0.4 mg daily before and during pregnancy; higher doses for those with a neural tube defect history or on valproic acid.
- Some ASMs may cause neonatal hemorrhagic disorder; evidence for prenatal vitamin K benefit is limited, but 10 mg/day is often given in the last month and/or at delivery to the newborn.
- Some ASMs enter breast milk—those with less protein binding accumulate more. ASM use isn't a reason to avoid breastfeeding, but ASM levels can be detected in infants.

Special Considerations in Patients of Asian and South Asian Descent

- Presence of the HLA-B*1502 variant increases SJS/TEN risk with carbamazepine, phenytoin, and oxcarbazepine in certain populations.
- HLA-B*1502 is most common in East Asian (6.9%), Oceanian (5.4%), and South/Central Asian (4.6%) populations, but less common in Japan (<1%) and Korea (<2.5%).
- HLA-A*3101 is linked to carbamazepine-induced skin reactions in Chinese, Japanese, and European populations; avoid carbamazepine in patients with this variant.
- Not all HLA-B*1502 or HLA-A*3101 positive patients develop SJS/TEN, and these reactions can still occur in negative patients of any ethnicity.

EVALUATION OF THERAPEUTIC OUTCOMES

- The goal of ASM therapy is seizure freedom or reduction, with minimal adverse effects.
- Monitor long term for seizure control, adverse effects, quality of life, medication interactions, and adherence. Clinical response is more important than serum drug concentrations.
- Monitor for long-term medication adverse effects such as osteoporosis.
- Screen periodically for mental health disorders (eg, anxiety and depression).
- Have patients and caregivers track seizure severity and frequency; regularly assess medication adherence.

See Chapter 79, Epilepsy by Viet-Huong V. Nguyen, Sunita Dergalust, and Edward Change for a more detailed discussion of the topic.

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